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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/765,672	01/27/2004	Kelly J. Henrickson	650053.91126	9828

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EXAMINER	
STAPLES, MARK	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 09/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/765,672	HENRICKSON ET AL.	
	Examiner	Art Unit	
	Mark Staples	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 52-63 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 52-63 is/are rejected.

7)☒ Claim(s) 53,57,60,and 63 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 01/27/2004.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. The instant application claims priority as a continuation of Ser. No. 09/484,704 filed Jan. 18, 2000, which is a continuation of Ser. No. 08/691,045, filed Aug. 1, 1996 (U.S. Pat. No. 6,015,664) which is a continuation-in-part of Ser. No. 08/552,907 filed Nov. 3, 1995 (U.S. Pat. No. 5,744,299).

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 08/552907, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Application No. 08/552907 fails to provide adequate support for the following element of claims 52-63: unequal

primer concentrations. Accordingly, claims 52-63 are not entitled to the benefit of the prior application, Application No. 08/552,907.

Information Disclosure Statement

2. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The title should reflect that the claimed invention is at least two target nucleic acids. The following title is suggested: "Methods of detecting the presence of target nucleic acids via a multiplex amplification reaction using unequal primer concentrations". Please also note the correction to plural for methods and concentrations.

The claimed invention is **not** a method for detecting the presence of a target nucleic acid but to at least two nucleic acids.

Claim Objections

4. Claims 53, 57, 60, and 63 are objected to because of the following informalities: the use of the singular of the word "primer" when the plural "primers" is correct. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 52-63 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps in claims 52, 55, 58, and 61 are: obtaining or isolating the nucleic acid, amplifying the target nucleic acids, conducting a control reaction, and measuring and comparing the amplification products to the control. While these claims recite the results of these steps, the active steps of the methods are missing.

Claims 52-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In these claims the use of the phrase "at least two primer pairs" creates confusion as to whether a reference to any two primers is a reference to two primers within a pair or two primers across pairs.

As claims 52, 55, 58, and 61 are written, they are indefinite since the clause "wherein the 5' primer and the 3' primer are in present in unequal concentrations" can mean the primers in one primer pair, or the 5' primer of one primer pair to the 3' primer of another primer pair. The following or similar is suggested: "wherein the 5' primer and the 3' primer of each primer pair are present in unequal concentrations".

As these claims 53, 57, 60, and 63 are written, they are indefinite since the clause "wherein the ratio of 5' to 3' primer[s] is selected from the group" can mean a ratio of primers in one pair of primers, or a ratio of a 5' primer of one primer pair to a 3' primer of another primer pair. The following or similar is suggested: "wherein the ratio of 5' to 3' primer[s] within each primer pair is selected from the group consisting of".

As claims 52, 55, 58, and 61 are written, they are indefinite since the clause "exposing a nucleic acid sample to at least two primer pairs specific for at least two target nucleic acids" can mean each primer pair is specific for at least two target nucleic acids, or each primer pair is specific to only one target nucleic acid. The following or similar is suggested: "exposing a nucleic acid sample with at least two target nucleic acids to at least two primer pairs, each primer pair being specific to only one of the said target nucleic acids".

As claims 52, 55, 58, and 61 are written, they are also indefinite since the claims do not give how the one concentration of paired primers, which are equal in concentration, relates to any concentration of paired primers, which are unequal in concentration. One might increase the formation of double stranded DNA simply by

using unequal concentrations each of which is higher than the one equal concentration. Clarification is needed.

As claims 52, 55, 58, and 61 are written, they are indefinite since the claims do not indicate whether optical density of these claims is a measurement specific to double stranded DNA, or whether, for example, it is a measurement of both single and double stranded DNA. Clarification is needed.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 52-54 and 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shyamala et al. (1989) in view of Wu et al. (EP0418960 A2 March 27, 1991).

Shyamala et al. teach forming double-stranded DNA product with unequal primer concentrations from a biological sample (entire reference, especially p. 1605, 2nd sentence under section *Sequencing of asymmetrically amplified fragments*: "A ratio of primer of 1:50 . . . results in synthesis of both a double-stranded fragment and of single-stranded DNA"). Shyamala et al. teach amplifying at least two nucleic acids: "The general applicability of this technique was shown by amplifying several other genes . . ." (see p. 1603, 6th sentence under the section *Amplification from chromosomal DNA*). Shyamala et al. teach using at least two pairs of primers (see Figure 1, 1st sentence in the legend). Shyamala et al. also teach that the "amplification product was visualized with ethidium bromide", a determination using optical density (see p 1603, last sentence under section *Amplification of bacterial chromosomal DNA by PCR*). Shyamala et al. teach comparing the unequal primer amplification yields more product than standard conditions of equal primer concentrations, that is, than control conditions of equal primer concentrations (see page 1603, 2nd sentence under the section *Asymmetric amplification of single-stranded DNA for direct sequencing of amplified product*). Shyamala et al. teach denaturing the DNA at least once at 93°C for 1 min (see p 1603, 3rd sentence under section *Amplification of bacterial chromosomal DNA by PCR*).

Regarding claims 58 and 59, the product being present at 3.59 times the amount produced with equal primer concentrations carries no patentable weight. This is a result of using the method and is not an active step of the method.

Although Shyamala et al. teach optical density, they do not teach measurement of optical density. Shyamala et al. do not teach primer ratios of 50:25, 25:50, 12.5:50 and 12.5:25.

Wu et al. teach a method of performing polymerase chain reaction using unequal primer concentration in which primer pairs is at least 2:1 or 50:25 (see abstract). Wu et al. further teach measuring amplification products with optical density (entire reference, especially use of spectrophotometers on page 6, line 20). As with Shyamala et al., Wu et al. also teach denaturation (see p. 7 line 37) and use of control amplification (see p. 7 line 40).

One of ordinary skill in the art would have been motivated to apply Wu et al.'s primer ratios and optical detection to Shyamala et al.'s method in order to successfully amplify double-stranded DNA. Wu et al. teach that unequal primer ratio of 2:1 and denaturation would lead to successful amplification and teach that the product can be measured by optical density. Thus, it would have been *prima facie* obvious to apply Wu et al.'s teachings to Shyamala et al.'s method in order to maximize and measure the amplification of double-stranded nucleic acid.

Claims 55-57 and 61-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shyamala et al. (1989) in view of Wu et al. (EP0418960 A2 March

27, 1991) and in further view of Karron et al. (J. Clinical Micro vol. 32 no. 2 pp. 484-88 1994).

Regarding claims 54 and 62, the product being present at 3.59 times the amount produced with equal primer concentrations carries no patentable weight. This is a result of using the method and is not an active step of the method.

Shyamala et al. teach as noted above.

Shyamala et al. do not teach at least two primers pairs specific for sequences selected from the group consisting of parainfluenza virus-1, 2 and 3, respiratory syncytial virus A and B and influenza virus A and B sequences.

Wu et al. teach as noted above.

Wu et al. do not teach at least two primers pairs specific for sequences selected from the group consisting of parainfluenza virus-1, 2 and 3, respiratory syncytial virus A and B and influenza virus A and B sequences.

Karron et al. teach PCR rapid detection of Parainfluenza virus type 3 of HN gene using RT-PCR by fluorescence (see whole doc. esp. abstract). Karron et al. teach at least two primers pairs specific for sequences selected from the group consisting of parainfluenza virus-1 (see p. 485, under the section *RT-PCR-EIA*, 3rd sentence for one primer pair, and 1st sentence of 2nd paragraph for a second primer pair).

Karron et al. do not teach unequal primer concentration. Karron et al. do not teach measuring the amplified product by optical density.

One of ordinary skill in the art would have been motivated to apply Wu et al.'s primer ratios to Karron et al.'s method in order to successfully amplify the virus nucleic

acid. Shyamala et al. in view of Wu et al. teach that unequal primer ratio of 2:1 would lead to successful amplification of double-stranded DNA, and thus it would have been *prima facie* obvious to apply Wu et al.'s ratios to Karron et al.'s method in order to maximize the amplification of viral nucleic acid.

Moreover, one of ordinary skill in the art would have been motivated to apply Wu et al.'s and Shyamala et al. teachings of optical detection to the fluorescence method of Karron et al. in order to successfully and quickly detect amplified virus by optical density. Thus, it would have been *prima facie* obvious to apply Wu et al.'s and Shyamala et al teachings of optical detection to Karron et al.'s detection method in order to rapidly detect viral sequences.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 52-63 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,015,664 in view of Wu et al. (EP0418960 A2 March 27, 1991).

Claims 54, 56, 59, and 62 carry no patentable weight, as they do not involve an active step of the method claims but are drawn to a result for the product being at least 3.59 times increased.

Regarding claims 55-57 and 61-63, Claim 1 is drawn to exposing nucleic acids to primer pairs specific for parainfluenza virus-1, 2 and 3, respiratory syncytial virus A and B and influenza virus A and B sequences wherein the primer are in unequal concentrations. Primer pairs encompasses at least two pairs of primers. Claim is drawn to "the nucleic acid or cDNA" and in the art cDNA is considered to be a collective noun for several nucleic acids, and thus claim encompasses at least two nucleic acids. Claim 1 can also be used two or more times to fulfill the element of at least two nucleic acids.

Regarding claims 52-54 and 58-60, Claim 1 is drawn as noted above, drawn to exposing a nucleic acid sample to primer pairs to target sequences, c DNA, and amplifying them. Claim 1 can also be used two or more times to fulfill the element of at least two nucleic acids.

Claim 1 is not drawn to a separate control reaction with equal primer pairs. Claim is not drawn to measurement of optical density. Claim 1 is not drawn to the specific primer ratios. Claim 1 is not drawn to denaturation.

Wu et al. teach a method of performing polymerase chain reaction using unequal primer concentration in which primer pairs is at least 2:1 or 50:25 (see abstract). Wu et al. further teach measuring amplification products with optical density (entire reference, especially use of spectrophotometers on page 6, line 20). Wu et al. also teach denaturation (see p. 7 line 37) and use of control amplification (see p. 7 line 40).

One of ordinary skill in the art would have been motivated to apply Wu et al.'s primer ratios, denaturation, and optical detection to the method claim of U.S. Patent No. 6,015,664 in order to successfully amplify double-stranded DNA. As Wu et al. teach that unequal primer ratio of 2:1 and denaturation would lead to successful amplification and teach that the product can be measured by optical density and compared to control prodcut, it would have been *prima facie* obvious to apply Wu et al.'s teachings to U.S. Patent No. 6,015,664 in order to maximize and measure the amplification of double-stranded nucleic acid.

Conclusion

7. No claim is free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Staples MS
Examiner
Art Unit 1637
September 5, 2006

KENNETH R. HORLICK, PH.D
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9/5/06